Pulmonary Artery Hypertension Specific Therapy Improves Exercise Tolerance and Outcomes in Exercise-Induced Pulmonary Hypertension

Brief title: Treatment in Exercise-Induced Pulmonary Hypertension

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Abnormal pulmonary vascular response to exercise can be a marker of early pulmonary arterial hypertension (PAH). We have previously demonstrated that the pressure-flow relationship of mean pulmonary artery pressure (mPAP) to cardiac output (CO) measurement could be applied to predict future development of overt PH in at-risk patients (e.g. scleroderma:SS) (1). The ΔmPAP/ΔCO can complement our understanding of early pulmonary vascular disease in at-risk patients, and help define abnormal pulmonary vascular response to exercise as an impaired pulmonary vascular capacity.

We sought to assess clinical worsening during long-term follow-up in at-risk patients and to evaluate whether vasodilator therapy improved pulmonary vascular response, exercise capacity and prognosis in exercise induced pulmonary hypertension (EIPH).

We designed a prospective, single-center, open-label, uncontrolled treatment trial of EIPH with PAH specific therapies in SS or mixed connective tissue disease (MCTD) with SS features. We prospectively performed 6 minute-walk (6MW) stress echocardiographic (SE) studies in 243 SS or MCTD patients with scleroderma features (1). For 6MW SE, we used an impedance-based device to measure CO, which was combined with tricuspid regurgitation-based right ventricular pressure, from which mPAP was estimated. Patients with non-EIPH based on our previous work (ΔmPAP/ΔCO≤3.3 and/or exercise mPAP≤25mmHg) were assigned only to the initial observational study. All patients with EIPH (ΔmPAP/ΔCO>3.3 and exercise mPAP>25 mmHg) received explanations for the exercise right heart catheter. We obtained informed consent for exercise RHC in 29 patients with EIPH.

At right heart catheter (RHC), EIPH was defined as mPAP at peak ≥30mmHg and pulmonary artery wedge pressure at peak <25mmHg during supine bicycle ergometer. After assessment of exercise RHC, patients with exercise were divided into two groups based on the

administration of PAH specific therapies (non-treatment and treatment groups). The composite outcome was time to clinical worsening. The efficacy end point was change in ΔmPAP/ΔCO and 6MW distance (6MWD) from baseline to one year.

The study population consisted of 243 patients. No EIPH was observed in 186 of 243 patients, and EIPH was observed in 57 of 243 patients in this cohort (**Table 1**).

During a median period of 4.3 years, 56 patients (23%) reached the composite outcome (death, n=3; unplanned hospitalization for worsening of PAH, n=12; worsening of World Health Organization functional class by at least one level and ≥15% decrease from baseline in 6MWD with increased PAP: n=41). Patients with EIPH had significantly shorter event-free survival than with non-EIPH. EIPH (HR,1.95; 95%CI [1.10–3.45]; p=0.023) was associated with time-to-event, independent of age, sex, and E/e'.

In patients with exercise RHC, 28 of 29 patients fulfilled the catheter criteria of EIPH. In our cohort, 14 of 29 patients received PAH specific therapies (treatment group) and 15 of 29 patients did not receive these therapies (control group) based on patient preference. There was no difference between control and treatment groups except for CO at rest.

6MWD was similar in patients with control and treatment groups at the beginning of the follow-up (p=0.69). At 1-year follow-up, treatment group had a trend of longer 6MWD than control group (p=0.09). ΔmPAP/ΔCO was also similar in patients with control and treatment groups at the beginning of the follow-up (p=0.30). At 1-year follow-up, treatment group had lower ΔmPAP/ΔCO than control group (p=0.02).

In RHC cases, 10 patients reached the composite outcome with only 1 died patient. The composite outcome occurred in 8% of the patients in the treatment group as compared with 36% of the patients in the control group (HR,0.25; 95% CI [0.06–0.97]; p=0.046).

We demonstrated that 57 of 243 patients at risk for PAH (due to SS or MCTD with SS features) with normal resting echocardiographic findings had EIPH based on an elevated ΔmPAP/ΔCO obtained by 6MW SE. Patients with EIPH had significantly shorter event-free survival than patients with non-EIPH. We note significant improvements in a number of post-treatment ΔmPAP/ΔCO patients compared to control values. Patients with EIPH who received treatment had longer event-free survival than who did not.

Patients with treatment received several pulmonary vasodilators. Based upon attending physician preference, the majority of our patients were treated with endothelin receptor antagonists (71%), which is similar to prior publications that primarily utilized ambrisentan therapy. Our results show that pulmonary vasodilators can improve exercise hemodynamics in general. We found that ΔmPAP/ΔCO improved significantly. These changes are results of lower vascular resistance after treatment. Intervention in early pulmonary vascular disease may improve endothelial function and subsequent distal vasculopathy.

In conclusion, patients with EIPH had significantly shorter event-free survival than patients with non-EIPH. This is the first study to demonstrate that early intervention in patients with EIPH diagnosed with 6MW SE may improve their pulmonary vascular distensibility and long-term outcomes.

References:1. Kusunose K, Yamada H, Hotchi J et al. Prediction of Future Overt Pulmonary Hypertension by 6-Min Walk Stress Echocardiography in Patients With Connective Tissue Disease. J Am Coll Cardiol 2015;66:376-84.

Table 1: Clinical data in entire cohort

Entire cohort	Non-EIPH	EIPH	p value
Number	186	57	
Age	57±13	62±12	0.003
Male, %	22 (12)	5 (9)	0.65
Body mass index	22±3	22±3	0.73
WHO Class I/II/III/IV	41/112/33/0	10/35/12/0	0.41
History			
SS, %	150 (81)	47 (82)	0.76
MCTD with SS features, %	36 (19)	10 (18)	0.76
Respiratory function			
%EFV1, %	80±20	85±15	0.42
%FVC, %	107±26	105±19	0.79
%DLCO	76±20	73±22	0.69
Baseline hemodynamics			
HR, bpm	69±11	69±11	0.93
Systolic BP, mmHg	122±19	126±21	0.19
Diastolic BP, mmHg	70±11	72±12	0.47
SpO_2, %	98±1	97±2	0.09
Post 6-min walk hemodynamics			
HR, bpm	91±17	91±17	0.93
Systolic BP, mmHg	126±23	133±28	0.14
Diastolic BP, mmHg	69±11	73±18	0.07
SpO_2, %	97±2	94±4	0.002
6MW distance, meter	446±95	439±85	0.59
Echocardiographic variables			
LVEDVi, ml/m^2	49±10	48±13	0.44
LVESVi, ml/m^2	17±4	19±5	0.24
LVEF, %	65±3	66±3	0.19
LAVi, ml/m^2	26±7	29±11	0.07
E/e'	7±2	8±4	0.02
RVEDA, cm^2	14±3	13±3	0.25
RVESA, cm^2	8±2	8±2	0.63
RVFAC, %	42±12	41±11	0.36
TAPSE, mm	22±4	22±4	0.63
Baseline echocardiographic hemodynamics			
TR-PG, mmHg	20±4	24±5	<0.001
Mean PAP, mmHg	17±3	19±3	<0.001
CO, l/min	4.0±1.1	3.7±1.3	0.21
Exercise echocardiographic hemodynamics			
Exercise TR-PG, m/sec	27±6	40±9	<0.001

Exercise mean PAP, mmHg	21±3	30±5	-
Exercise CO, l/min	6.4±2.4	5.4±1.6	<0.001
ΔTR-PG	7±4	16±7	<0.001
ΔmPAP	5±2	10±4	<0.001
ΔCO	2.4±1.9	1.6±0.8	<0.001
ΔmPAP/ΔCO, mmHg/l/min	2.8±2.6	7.6±6.2	-
Outcomes	Hazard ratio	95% CI	
EIPH	1.95	1.10-3.45	0.023**
Exercise right heart catheter group only	**Control**	**Treatment**	
Number	15	14	
Age	63±12	59±14	0.42
Male, %	1 (7)	1 (7)	0.96
History			
SS, %	13 (87)	10 (71)	0.33
MCTD with SS features, %	2 (13)	4 (19)	0.33
Medication			
PDE5 inhibitors, %	0	3 (22)	-
ERA, %	0	10 (71)	-
PGI2, %	0	1 (7)	-
Right heart catheter			
mPAP at rest, mmHg	20±4	21±4	0.36
mPAP during exercise, mmHg	39±6	42±9	0.29
PAWP at rest, mmHg	9±3	10±3	0.49
PAWP during exercise, mmHg	16±3	17±3	0.43
CO at rest, l/min	6.0±1.7	4.8±1.1	0.03
CO during exercise, l/min	9.7±2.6	8.4±2.3	0.16
PVR at rest, wood unit	1.9±0.8	2.6±1.1	0.07
PVR during exercise, wood unit	2.5±0.5	3.1±0.8	0.06
Baseline			
6MWD, meter	426±82	454±65	0.69*
ΔmPAP/ΔCO, mmHg/l/min	5.7±2.7	6.8±2.9	0.30*
At the 1 Year Follow-up			
6MWD, meter	415±83	478±55	0.09*
ΔmPAP/ΔCO, mmHg/l/min	6.8±3.2	4.4±2.7	0.02*
Outcomes	Hazard ratio	95% CI	
Treatment	0.25	0.06-0.97	0.046†

Data are presented as number of patients (percentage) and mean ± SD.

Abbreviations: EIPH, exercise-induced pulmonary hypertension; WHO, world health organization; SS, scleroderma; MCTD, mixed connective tissue disease, %FEV1, percent forced

expiratory volume in 1 s; %FVC, percent forced vital capacity; %DLCO, diffusing capacity for carbon monoxide; HR, heart rate; BP, blood pressure; SpO_2, percutaneous oxygen saturation, LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LAVi, left atrial volume index; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular motion; RVEA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular functional area change; TAPSE, tricuspid annular plane systolic excursion; TR-PG, tricuspid regurgitant pressure gradient; mPAP, mean pulmonary artery pressure; CO, cardiac output; PDE5 inhibitors; phosphodiesterase type 5 inhibitors, ERA; endothelin receptor antagonists; PGI2, prostacyclin; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; CI, confidence interval.

*: p value on the basis of mixed effect model.

**: p value on the basis of Cox proportional hazard model after adjustment of age, sex, and E/e'.

†: p value on the basis of Cox proportional hazard model